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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/960,557	10/31/1997	EUGENIO A. CEFALI	SD-50003USP6	6174

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1611	

NOTIFICATION DATE	DELIVERY MODE
09/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_Abbott_Park@abbott.com

Office Action Summary	Application No.	Applicant(s)	
	08/960,557	CEFALI ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,32,35,36,38,41,42,44,62 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,32,35,36,38,41,42,44,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of response dated 7-15-10 is acknowledged.

Claims 29, 30, 32, 35-36, 38, 41-42, 44 and 62-63 are pending.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 29, 30, 32, 35, 36, 38, 41, 42, 44, 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,260,305 to Dennick in view of either US 5,126,145 to Evenstad et al ('145), Saito et al (Arteriosclerosis and Thrombosis, 1991) or US 5,126,145 to Evenstad et al ('145), US 5,116,10 to Broaddus (‘610) and Saito et al (Arteriosclerosis and Thrombosis, 1991).

3. Dennick teaches a combination of cholesterol lowering drugs that include niacin, of the instant claims, for effectively lowering cholesterol levels, such as LDL and for treating hyperlipiemia (col. 2). Dennick teaches niacin in an amount ranging 75 mg to 2000 mg (col. 3, L 49-63), in a single or divided dosage forms. For the claimed swellable polymers, Dennick gelatin, starch etc (col. 4, L 37-40). While Dennick does not state 1500 mg in a single dose, the range of 75 -2000mg includes the claimed 1500 mg because Dennick teaches starting with a low dose and working up to higher concentrations so as to achieve a desired effect (col. 3, l 64-67). Thus, administering a

dose of 1500 mg would have been within the scope of a skilled artisan with an expectation to achieve the desired treatment for elevated cholesterol levels.

4. Dennick does not exemplify a composition comprising niacin and a swelling polymer such as HPMC or those recited in claim 62. Dennick also fails to teach administering at evening or night.

5. '145 teach sustained or controlled release tablets comprising 250, 500 or 750 mg niacin (col. 5, l.54-55). The tablets of '145 comprise 5-30 wt.% hydroxypropyl methylcellulose (HPMC) (col. 3, l.18-39), 2-5 wt.% binders (i.e. PVP, starch, gelatin, sucrose, lactose, methylcellulose, HPMC having binding properties and the like) (col. 3, l.40 through col. 4, l.12), 2-20 wt.% hydrophobic component (preferably stearic acid and hydrogenated vegetable oil) (col. 4, l.13 through col. 5, l.9), lubricants, dyes, fillers and extenders (col. 5, ll. 10-36). '145 further teach that the dissolution profile of the tablets is 10-35% release in 2 hours after oral ingestion, 40-70% in 8 hours, and at least 90% in 24 hours (col. 5, l1.66 through col. 6, H. 5).

6. '610 teach an oral composition comprising cholestyramine and polyol polyesters for reduced cholesterol levels and in the treatment of hypercholesterolemia (col. 2). '610 teach the compounds in the form of tablets (col. 2). For the treatment, '610 suggests that administering the drug at evening before meals or bed time is preferred (col. 6, L 18-20) for effective reduction in cholesterol levels.

7. Saito et al studied a comparison between morning and evening doses of simvastatin in hyperlipidemic subjects and observed that once-a-day evening oral doses of simvastatin reduced cholesterol levels in the subjects greater than when the drug was

given in the morning (abstract, pages 825). Saito states that there is circadian variation in the biosynthesis of cholesterol and that the biosynthesis activity is accelerated at night (lines bridging pages 816-817).

8. It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare a controlled release oral composition comprising the active agents of Dennick by employing a cellulose such as HPMC because '145 suggests that HPMC is a known controlled release material that hydrates on the surface of a tablet to form a gel layer, which contributes to the controlled release characteristics of the drug and provides the desired release rate (col. 1-3). Further, '145 teach the amount of HPMC in the same range as that described in the instant specification. A skilled artisan would have expected to achieve a desired rate release of niacin by controlling the release of the drug from a composition containing niacin along with a swellable polymer, HPMC.

9. Further, a skilled artisan would have been motivated to administer the niacin composition of Dennick at evening or night suggested by '610 or Saito because both references suggest administering at evening or bed time is safe and effective and further Saito teaches that due circadian rhythms the cholesterol biosynthesis is more at night and therefore administering when at the time when the cholesterol synthesis is high is effective in reducing cholesterol levels and thus controlling the levels of serum cholesterol (page 824, col. 1). Thus, a skilled artisan would have expected to achieve the balance of cholesterol levels without any associated side effects such as hepatotoxicity and yet a prolonged release of niacin in the composition of Dennick.

Response to Arguments

10. Applicant's arguments filed 7-15-10 have been fully considered but they are not persuasive.

11. Applicants' argue that instant claims are directed to a method of orally administering to a patient once per day during the evening or at night at least two intermediate release formulations of nicotinic acid and a swelling agent to obtain a dose of at least 1500 mg nicotinic acid, with a particular in vitro dissolution profile and that the combination of Dennick in view of Evenstad and Saito, as well as the combination of Dennick in view of Evenstad, Saito, and Broaddus, do not disclose each and every element of the claimed invention, and one skilled in the art would have no motivation to combine the teachings of the various references. Applicants argue that the novelty of the instant claims lies in the once-a-day administration of an intermediate release formulation, in the evening with minimal hepatotoxicity, which is not taught by the references. Applicants' argue that although Dennick teaches that the combination of pravastatin and nicotinic acid may be administered once daily, a skilled artisan would interpret their teaching as directed to a combination regimen whereby pravastatin is administered once daily and nicotinic acid is administered twice a day (col. 6, l 35-40). Applicants argue that Evenstad teaches a sustained release tablet and is designed fro dosing twice a day and teaches scored tablets for breaking into smaller doses of up to 750 mg twice daily.

12. Applicants' arguments are not persuasive because a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art,

including nonpreferred embodiments. Merck & Co. v.Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); and Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). In this regard, Dennick not only teaches 1g quantities of NA, but also suggests upto 3000 mg, either in a single or a divided dose. Hence, a skilled artisan would have been able to administer upto 3000 mg of nicotinic acid either in divided doses thus arriving at "at least 1500 mg (as claimed)" from the teachings of Dennick.

13. It is argued that Dennick lacks an intermediate release formulation and instead teaches only extended release version (col. 6, L 35-40) and fails to recognize that the extended release composition results in greater liver toxicity, as described in McKenney et al. JAMA 1994; 271(9):672-7. It is argued that instant methods overcome such a problem by requiring 40-60% nicotinic acid to be released from the claimed formulation after 9 hrs. It is argued that instant dissolution profiles are different from sustained release and is intermediate to that of the currently commercially available formulation. It is argued that because Dennick fails to disclose that sustained or extended release nicotinic acid formulations are hepatotoxic, and in fact teaches the desirability of using a sustained release formulation, one of ordinary skill in the art would not have been motivated to arrive at the instantly claimed subject matter. Applicants' arguments are not persuasive because instant claims do not recite absence of hepatotoxicity and moreover, Dennick desires compositions that do not have side effects. Applicants argue that it cannot be said that Dennick teaches an administration of once per day. However,

Dennick states that the active agents may be given in doses of one to four times daily (col. 3, L 64-68). With respect to Evenstad, the reference has been cited for the teachings of a swellable polymer and the time of administration of niacin (evening or night). However, the examiner also notes that instant specification describes dissolution profiles (tables 4) that are also described by Evenstad (figure I of the reference). According to the instant specification, doses of 250, 375, 500, 750 and 1000 mg have a similar dissolution profiles (table 4) and admittedly Evenstad teaches doses upto 750 mg, which have the same release profiles as that in table of 4 the instant disclosure. Thus, a skilled artisan would be able to expect to modify the tablet of Dennick with the swellable polymer of Evenstad and administer the composition in the evening or at night so as to achieve the release profile taught by Evenstad, which meets the instant release rates.

14. Applicants argue that neither Saito nor Broaddus remedy the deficiencies of Dennick, as they do not teach nicotinic acid and rather focus on other cholesterol-lowering substances. It is argued that the references do not suggest any formulations with safety profile and the safety profile of the drugs taught by Saito and Broaddus is different from the safety-profiles of instant formulation. Hence it is argued that instant specification shows no liver toxicity with the claimed composition. Applicants' arguments are not persuasive because even though neither Saito nor Broaddus teach compounds other than niacin, Dennick teaches a combination of niacin and pravastatin. In this regard, Saito teaches administration of statin compounds (related to pravastatin of Dennick) and further the fact that in general drugs treating hyperlipidemia are

administered at evening or night comes from both Saito and Broaddus. Particularly, according to Saito, there is a circadian variation in the biosynthesis of cholesterol, and the biosynthetic activity is accelerated during the night (page 816, col. 2). Therefore, even though Saito (as well as '610) teaches a different drug, a skilled artisan would readily recognize from Saito as well as '610 that it is based on the condition (hyperlipidemia) that one has to administer an anti-hyperlipidemic drug at an appropriate time such that the maximum effect of the drug to interfere with elevated levels of cholesterol or its biosynthesis are effective (page 824). This is further supported by the teachings of '610. Accordingly, even though Dennick and Evenstad do not recognize the claimed balanced lipid alteration, a skilled artisan would be able to control the release of the drug (niacin) from HPMC and also see a balanced lipid alteration because the motivation to administer the composition at night or evening comes from the teachings of Saito or Broaddus, in addition to the teachings of Evenstad.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611